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A multicenter, randomized, double-blind dose-ranging study of glycopyrrolate/formoterol fumarate fixed-dose combination metered dose inhaler compared to the monocomponents and open-label tiotropium dry powder inhaler in patients with moderate-to-severe COPD



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ABSTRACT

Background: This study formed part of the dose selection for a glycopyrrolate (GP)/formoterol fumarate (FF) fixed-dose combination formulated using novel Co-Suspension™ Delivery Technology and delivered via a metered dose inhaler (GFF MDI). The study aimed to confirm the optimal dose of GP to formulate with FF 9.6 µg in the fixed-dose combination product, GFF MDI.

Methods: This multicenter, randomized, double-blind, chronic-dosing, balanced incomplete block, crossover study (NCT01587079) compared five doses of GFF MDI (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6 and 1.2/9.6 µg, twice daily [BID]) with its monocomponents FF MDI 9.6 µg and GP MDI 18 µg (both BID) and open-label tiotropium (18 µg once daily) as the active control. The primary efficacy endpoint was change from baseline in forced expiratory volume in 1 s area under the curve from 0 to 12 h (FEV₁ AUC_{0–12}) on Day 7.

Results: In total, 159 patients were randomized to treatment and 132 patients (52.2% male, mean age 62.8 years) were included in the intent-to-treat population. All doses of GFF MDI (except 1.2/9.6 µg) resulted in statistically significant improvements in FEV₁ AUC_{0–12} versus monocomponents and open-label tiotropium. GFF MDI 18/9.6 µg consistently showing the greatest improvement over monocomponents and open-label tiotropium. Adverse events for each GFF MDI dose were similar versus GP MDI 18 µg, FF MDI 9.6 µg and open-label tiotropium.

Conclusions: These findings further support selection of GP 18 µg as the optimal dose to combine with FF MDI 9.6 µg for advancement into Phase III clinical trials of GFF MDI.

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Abbreviations

AE	adverse event
AUC _{0–12}	area under the curve from 0 to 12 h
BID	twice daily
CAT	COPD Assessment Test
CT	computerized tomography
DPI	dry powder inhaler
ECG	electrocardiogram
FDCs	fixed-dose combinations
FEV ₁	forced expiratory volume in 1 s
FF	formoterol fumarate
FVC	forced vital capacity
GFF	glycopyrrolate/formoterol fumarate
GP	glycopyrrolate
HFA	hydrofluoroalkane

IC	inspiratory capacity
ICS	inhaled corticosteroid
ITT	intent-to-treat
LABA	long-acting β_2 -agonist
LAMA	long-acting muscarinic antagonist
MDI	metered dose inhaler
mITT	modified intent-to-treat
PEFR	peak expiratory flow rate
pMDI	pressurized metered dose inhaler
PK	pharmacokinetics
SAE	serious adverse event
SMI	Soft Mist™ Inhaler
SVC	slow vital capacity
TEAE	treatment-emergent adverse event
URTI	upper respiratory tract infection

1. Introduction

Long-acting inhaled bronchodilators are central to the maintenance treatment of chronic obstructive pulmonary disease (COPD). They are recommended as first-line therapy for most patients with COPD, except those with few symptoms, only mild-to-moderate airflow limitation and infrequent exacerbations [1]. Two major classes of long-acting inhaled bronchodilators are available for the treatment of COPD, namely long-acting β_2 -agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) [2].

The distinct and complementary mechanisms by which LABAs and LAMAs induce bronchodilation provide a robust rationale for combining these two classes of bronchodilators [3]. Both classes of bronchodilators induce airway smooth muscle relaxation; LAMAs by inhibiting the M3 receptor and LABAs by activating β_2 -adrenoceptors [3]. For patients with COPD whose symptoms are not adequately improved by a single long-acting inhaled bronchodilator, the combined use of a LABA and a LAMA is recommended to achieve greater bronchodilation and symptom improvement while at the same time reducing the risk of side effects from increasing the dose of a single bronchodilator [1].

For greater convenience in administering dual long-acting bronchodilator therapy, several fixed-dose combinations (FDCs) of different LAMA and LABA agents in single-delivery devices are in development or have recently become available [4]. These devices differ in their design and delivery characteristics and include single- and multi-dose dry powder inhalers (DPIs) [5–10], the Soft Mist™ Inhaler (SMI) [11] and a hydrofluoroalkane (HFA)-propelled pressurized metered dose inhaler (pMDI) [12–14]. In order to overcome the formulation challenges presented by drug delivery via HFA pMDIs, particularly of products in combination, a new Co-Suspension™ Delivery Technology has been developed to allow the aerosol delivery of micronized drugs suspended with micro-sized, spray-dried, phospholipid-based porous particles [15–17].

Co-Suspension delivery technology has been used to develop LAMA glycopyrrolate (GP; also known as glycopyrronium bromide) and LABA formoterol fumarate (FF) HFA-propelled MDIs, both as single and combination products in different doses. GP and FF delivered as single therapies are well-tolerated and improve lung function, hyperinflation, rescue medication use, COPD symptoms, and quality of life versus placebo [18–25].

Previous studies with GP and FF using Co-Suspension delivery technology have demonstrated minimal dose-to-dose variability, a high fine-particle fraction and favorable aerodynamic properties

in vitro leading to reduced simulated oropharyngeal deposition [26–28]. In addition, the aerodynamic particle size distribution of the individual components within the combination products has been shown to be essentially the same as that of the individual components [26]. Furthermore, the pharmacokinetics (PK) of the individual components within the combination has been unaffected by combining them within the same device [29]. A previous randomized dose-ranging study of FF in this device showed that the efficacy, safety and PK of a dose of 9.6 μ g was comparable to the approved dose of formoterol (12 μ g) in a DPI (Foradil® Aerolizer®, Novartis International AG, Basel, Switzerland) [25]. Moreover, a previously performed dose-ranging study of GP in this device identified the optimal dose of GP MDI as 18 μ g (equivalent to glycopyrronium 14.4 μ g) [30]. The present study assessed the incremental benefit of a range of doses of GP when added to FF 9.6 μ g in an FDC (GFF MDI) in patients with moderate-to-severe COPD (NCT01587079). An additional objective was to confirm that the previously identified optimal dose of GP MDI administered as a single agent provided optimal bronchodilation when combined with FF MDI 9.6 μ g.

2. Methods**2.1. Patients**

Patients were eligible if they were ≥ 40 and ≤ 80 years of age with an established history of moderate-to-severe COPD, as defined by the American Thoracic Society (ATS) [31] and a smoking history of ≥ 10 pack-years. Moderate-to-severe COPD was confirmed at screening by a post-bronchodilator forced expiratory volume in 1 s (FEV₁)/forced vital capacity (FVC) ratio < 0.70 and a percent post-bronchodilator FEV₁ $\geq 30\%$ and $< 80\%$ predicted normal value calculated using the Third National Health and Nutrition Examination Survey (NHANES III) reference equations. Patients were required to have a chest X-ray or computerized tomography (CT) scan that was acceptable to the Investigator, within 6 months prior to screening. Patients who had a chest X-ray or CT scan that revealed clinically significant abnormalities not believed to be due to the presence of COPD were not enrolled. Reversibility to albuterol HFA (salbutamol; Ventolin®, GlaxoSmithKline plc, Brentford, United Kingdom) and COPD Assessment Test (CAT) score [32,33] were used to provide demographic data on the patient population and/or allow categorization by disease severity and symptoms, but not to determine eligibility for the study. Patients were required

to provide written, informed consent.

Patients were excluded if they had a current diagnosis of asthma, α_1 -antitrypsin deficiency or other respiratory disorder, had FEV₁ <0.750 L, had used systemic corticosteroids or antibiotics, or had been hospitalized due to exacerbation of COPD or a lower respiratory tract infection within 3 months prior to screening. Patients were also excluded if they had an abnormal 12-lead electrocardiogram (ECG) that was indicative of an active medical problem. Pregnant or nursing (lactating) women and women of childbearing potential, unless using acceptable methods of contraception, were excluded. Other exclusion criteria included use of long-term oxygen therapy, or regular use of short-acting bronchodilators, including nebulized therapy.

Prohibited therapies for COPD included inhaled or oral LABAs, inhaled corticosteroid (ICS)/LABA FDCs, phosphodiesterase inhibitors, mast cell stabilizers, leukotriene antagonists or tiotropium (only available LAMA at time of the study). Patients who met all entry criteria but were using prohibited medications had the prohibited medications discontinued for the duration of the trial, and were switched to two inhalations of ipratropium bromide (Atrovent®, Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany) MDI four times daily during the screening and washout periods. All patients underwent a washout period of ≥ 7 days (14 days if taking tiotropium or phosphodiesterase inhibitors). Patients receiving a maintenance dose of an ICS as part of a FDC containing fluticasone/salmeterol, mometasone/formoterol, or budesonide/formoterol were required to have been on the ICS component and maintained on a stable dose for at least 4 weeks prior to screening. These patients were switched to the corresponding dose of fluticasone, mometasone or budesonide administered twice daily (BID) as a single agent with ipratropium HFA MDI (Atrovent®) administered four times daily during the screening and washout periods. Patients receiving a maintenance dose of an ICS that was not administered as a FDC together with a LABA were permitted to continue the ICS provided they had been maintained on a stable dose for at least 4 weeks prior to screening.

2.2. Study design and treatment

This was a multicenter, randomized, double-blind, chronic dosing, balanced incomplete block, crossover study conducted at 20 sites in the USA (Supplementary Fig. 1). There were eight study medications in total: GFF MDI at five different ex-actuator doses: 18/9.6 μg (equivalent to glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg), 9/9.6 μg , 4.6/9.6 μg , 2.4/9.6 μg , and 1.2/9.6 μg ; its monocomponents FF MDI 9.6 μg and GP MDI 18 μg , as well as open-label tiotropium 18 μg DPI (Spiriva® HandiHaler®, Boehringer Ingelheim Pharma GmbH & Co KG, Ingelheim am Rhein, Germany) as an active comparator. Two inhalations of GFF, GP, or FF were administered BID from non-distinguishable MDIs. The patient, clinical site personnel and Pearl Therapeutics Inc. were unaware of the treatment dose assigned to a patient when the treatment was GFF MDI, GP MDI, or FF MDI. One dose of tiotropium was administered once per day in the morning via the HandiHaler®. Blinding with regard to the open-label tiotropium was not performed, so all personnel and patients were aware of treatment with the active control.

Following screening, patients were randomized using an interactive web response system to one of 56 unique sequences. Each sequence included four of the eight possible treatments, each administered for 7 consecutive days (Supplementary Fig. 1). On Day 1 of each treatment period, patients administered their first dose at the clinic under site personnel supervision and remained at the clinic until completion of all protocol-defined assessments, up to and including 2-h post-dose time point. Patients were then discharged from the clinic and continued to administer their study

medication at home. On Day 7, at approximately the same time as on Day 1, patients returned to the clinic where they received their last dose of that treatment period and remained until they had completed all protocol-defined assessments, up to and including the 12-h post-dose time point. Patients then underwent a 7- to 21-day wash-out period before starting the next treatment block.

All COPD medications, including study medication, rescue medication and ICSs, were withheld for at least 6 h prior to each visit, or the visit was rescheduled as soon as practical but within the specified visit windows. During the study, albuterol MDI (Ventolin®) was permitted as needed for relief of symptoms. During the screening phase and washout periods between treatments ipratropium MDI (Atrovent®) four times daily was used as maintenance medication, but was withheld for at least 6 h before each study visit.

Medications that may have an impact on efficacy or safety were not permitted during study participation and included non-selective β -adrenoreceptor antagonists, tricyclic antidepressants, monoamine oxidase inhibitors, anticonvulsants and phenothiazines.

This study was conducted in accordance with International Conference on Harmonisation guidelines [34], the Declaration of Helsinki and the US Code of Federal Regulations.

2.3. Assessments

Patients attended clinic visits at screening (Visit 1), the first day of each treatment period (Visits 2 [randomization], 4, 6 and 8) and the seventh day of each treatment period (Visits 3, 5, 7 and 9) (Supplementary Fig. 1). Visit 10 was the final/follow-up visit. Subjects completed all post-study assessments, including a final physical examination and recording of any adverse events (AEs), and were then discharged from the study.

All pulmonary function tests including FEV₁, FVC, peak expiratory flow rate (PEFR), slow vital capacity (SVC) and inspiratory capacity (IC) as defined in ATS/European Respiratory Society (ERS) guidelines were performed in accordance with ATS/ERS criteria [35]. Spirometry was performed to assess lung function pre- and post-dose at each study visit. The assessed time points on Day 1 of each treatment period were 60 and 30 min pre-dose and 15, 30, 60 and 120 min post-dose. On Day 7, an increased number of post-dose time points were assessed: 15, 30, 60 and 120 min, followed by every 2 h up to the final time points of 11.5 h and 12 h post-dose.

Diaries were provided to maintain a daily record of study drug administration, use of rescue medication and home PEFR measurements.

The safety assessments undertaken at screening and each visit included ECGs, vital signs, physical examination findings, clinical laboratory tests, monitoring for paradoxical bronchospasm (defined as a reduction in FEV₁ of >20% from test day baseline accompanied by: wheezing, shortness of breath or cough) and assessment of symptoms of dry mouth and tremor (patients were specifically questioned), in addition to AEs and serious AEs (SAEs). In addition, regular monitoring of hematology, blood chemistry and urine, vital signs (pulse rate, blood pressure), physical condition and body weight were assessed. ECG measurements were also made before and after administering the study drug. On Day 1 of each treatment period (Visits 2, 4, 6, and 8), ECGs were taken between 1 and 2 h and between 30 min and 1 h prior to study drug and at 15 and 30 min, 1 and 2 h after study drug. On Day 7 of each treatment period (Visits 3, 5, 7, and 9), ECGs were obtained between 1 and 2 h and between 30 min and 1 h prior to study drug and at 15 and 30 min, 1, 2, 4, and 12 h after study drug. Original ECGs with interval printouts and rhythm strip run at 25 mm/s were provided with the appropriate electronic case report form.

2.4. Endpoints

The primary efficacy outcome was the change from baseline in FEV₁ area under the curve from 0 to 12 h (FEV₁ AUC_{0–12}) on Day 7 of each treatment period, following chronic dosing. FEV₁ AUC_{0–12} values were based on nominal measurement times, and was normalized by the nominal total period of evaluation (12 h). Each dose of GFF MDI was compared with GP MDI, FF MDI, and open-label tiotropium.

Secondary endpoints evaluated on Day 1 of each treatment period were peak change in FEV₁ from baseline (defined as the highest change post-dose during the 2-h post-dose time period on Day 1), time to onset of action, proportion of patients achieving $\geq 12\%$ improvement in FEV₁, and peak change in IC from baseline. On Day 7 of each treatment period, secondary endpoints collected included change from baseline in morning pre-dose FEV₁, peak change in FEV₁ through 6 h, peak change in IC, and mean evening 12-h post-dose trough FEV₁.

Pre- and post-dose morning and evening assessments of PEFR were collected by patients at home and recorded in the patient diary. At each study visit, the Investigator reviewed the PEFR readings. PEFR immediately before and 30 min after dosing with study medication was also recorded in the clinic at each treatment visit (Visits 2 through 9).

2.5. Statistical analysis

A sample size of 160 was calculated to provide approximately 89% power to detect a difference in FEV₁ AUC_{0–12} of 0.080 L allowing for an anticipated drop-out rate of 9% in each treatment period.

Primary efficacy analyses were conducted using the modified intent-to-treat population (mITT), which included all patients that completed at least two treatment periods and excluded data affected by major deviations determined prior to database lock and un-blinding. AUC was calculated using trapezoidal integration on the available time points. FEV₁ measurements were placed into nominal time windows based on the number of minutes or hours they were from the time of the study medication dose and used to calculate AUC.

The analysis of the primary efficacy endpoint (FEV₁ AUC_{0–12} relative to baseline), involved two *a priori* treatment comparisons for superiority for each of the five doses of GFF MDI compared with the individual components, GP MDI 18 μ g and FF MDI 9.6 μ g, using a two-sided significance level of 0.05. These comparisons were made using a linear mixed-effects model with covariates of baseline pre-dose FEV₁, percent reversibility, period, sequence and treatment as fixed-effects and patient as a random effect. Type I error was controlled for each dose of GFF MDI by requiring that the dose be statistically significantly superior to both individual components. Assessment across doses of GFF MDI was made to aid in the selection of a final dose for Phase III.

Similar analyses were performed for secondary endpoints with the exception of percent responder analyses that used logistic regression. Time to onset was defined as the first post-baseline time when a $\geq 10\%$ improvement (increase) in FEV₁ was seen relative to the baseline value.

The safety population was defined as patients who were randomized, received at least one dose of a study treatment and had a post-baseline safety assessment for that treatment. AEs were summarized by the number of patients within a given treatment group, tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and the MedDRA System Organ Class.

3. Results

3.1. Patient disposition and baseline characteristics

The patient disposition is shown in Fig. 1 and demographic characteristics of the intent-to-treat (ITT) population are presented in Table 1. Overall, most (96%) patients were Caucasian, and just over half were male (52%). Patients had a mean age of 63 years, a mean body mass index of 28 kg/m², a mean smoking history of 55 pack-years and, on average, moderate airflow limitation (mean post-bronchodilator FEV₁ 55% predicted). Of the 159 randomized patients, 132 completed ≥ 2 treatment periods that included Day 7 data (modified intent-to-treat [mITT] population). In the mITT population, 63, 56, 61, 61, 65, 60, 62, and 63 patients received GFF MDI 18/9.6 μ g, GFF MDI 9/9.6 μ g, GFF MDI 4.6/9.6 μ g, GFF MDI 2.4/9.6 μ g, GFF MDI 1.2/9.6 μ g, GP MDI 18 μ g, FF MDI 9.6 μ g, and open-label tiotropium 18 μ g, respectively.

3.2. Efficacy

3.2.1. Primary efficacy endpoint

Adjusted mean change from baseline in FEV₁ (L) at each time point over 12 h post-dose for each treatment on Day 7 are illustrated in Fig. 2, and the adjusted mean differences in FEV₁ AUC_{0–12} between each GFF MDI dose combination and each mono-component at Day 7 in Fig. 3. GFF MDI showed dose-ordered improvements in FEV₁ AUC_{0–12} that were significant for all doses compared with GP MDI 18 μ g, FF MDI 9.6 μ g and open-label tiotropium 18 μ g, except for GFF MDI 1.2/9.6 μ g (Fig. 3; Supplementary Table 1). Moreover, the improvement in FEV₁ AUC_{0–12} for GFF MDI 18/9.6 μ g was greater than that for all lower doses of GFF MDI.

3.2.2. Secondary efficacy endpoints evaluated on day 1

All GFF MDI doses provided >0.300 L peak change in FEV₁ from baseline on Day 1 without any clear dose-ordered effect from a dose of 18/9.6 μ g down to 2.4/9.6 μ g (Fig. 4a; Supplementary Table 2). Moreover, the peak increases in FEV₁ from baseline were significantly greater than those observed for GP 18 μ g and open-label tiotropium 18 μ g for all doses of GFF ($p < 0.001$) but not significantly greater than those for FF MDI 9.6 μ g (Fig. 4a).

The majority of patients receiving GFF MDI (51–66%) or FF MDI (60%) had an onset of action ($\geq 10\%$ improvement in mean FEV₁ from baseline) within the 15-min endpoint. A smaller percentage of patients receiving GP or open-label tiotropium exhibited this rapid onset (27% and 37%, respectively).

A higher percentage of patients (93%) achieved at least 12% improvement in FEV₁ on the first day of treatment with the largest dose of GFF MDI than with any of the lower doses (83–86%) or either of the individual components (GP MDI 18 μ g 56%; FF MDI 9.6 μ g 80%; open-label tiotropium 72%).

All doses of GFF MDI showed peak increases in IC that were ≥ 0.320 L and significantly higher than those observed for GP MDI or, with the exception of GFF 9/9.6 μ g, for open-label tiotropium. However, none of the doses of GFF MDI showed significantly greater peak increases in IC compared with FF MDI 9.6 μ g on Day 1 (Supplementary Table 3; Supplementary Fig. 2).

3.2.3. Secondary efficacy endpoints evaluated on day 7

All treatments achieved >0.100 L improvement in morning pre-dose trough FEV₁ compared with baseline; the greatest improvement was observed for the highest dose of GFF MDI (0.183 L; 95% CI 0.151, 0.216) (Supplementary Table 4). Only GFF MDI 18/9.6 μ g and GFF MDI 2.4/9.6 μ g showed a significantly greater improvement from baseline in morning trough FEV₁ than GP MDI 18 μ g and open-label tiotropium 18 μ g, while all but the lowest dose of GFF MDI

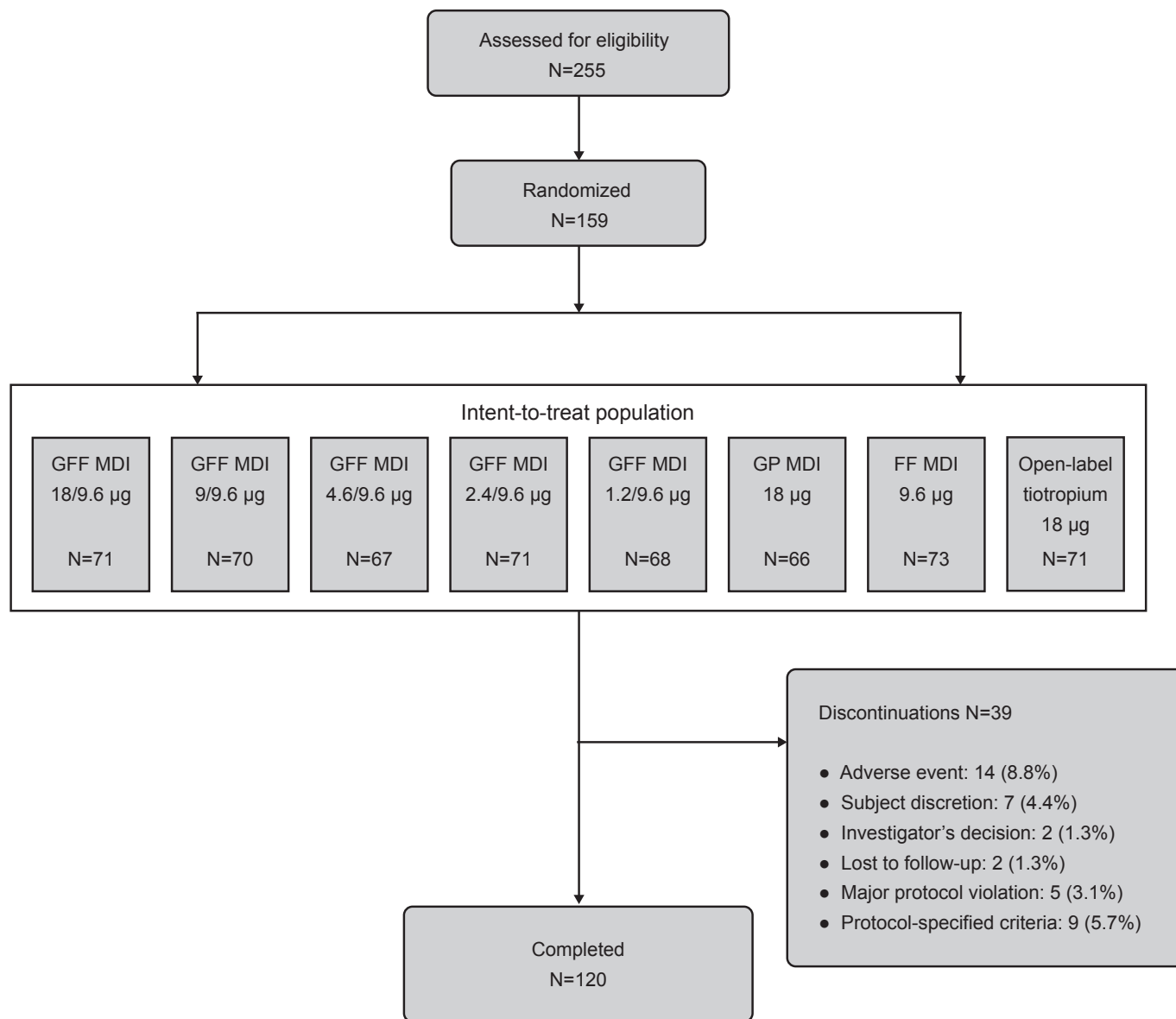


Fig. 1. Patient disposition throughout the study: Of 159 patients who were enrolled and randomized, 120 patients completed the study. FF, formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; GP, glycopyrrolate; MDI, metered dose inhaler.

demonstrated significantly greater improvements than FF MDI 9.6 µg (Fig. 4b).

Peak change in FEV₁ over 6 h post-dose on Day 7 ranged from 0.363 L with GFF MDI 1.2/9.6 µg to 0.444 L with GFF MDI 18/9.6 µg, versus 0.300, 0.332 and 0.309 L for GP MDI, FF MDI and open-label tiotropium, respectively (Supplementary Table 5). All doses of GFF MDI showed significantly greater peak increases versus GP MDI and open-label tiotropium, as did all doses except 1.2/9.6 µg versus FF MDI.

Peak change from baseline in IC ≥ 0.368 L (range 0.368–0.441 L) for all doses of GFF MDI compared with smaller improvements with GP MDI 18 µg (0.223 L) and open-label tiotropium (0.241 L) with the numerically largest changes observed for the two highest doses of GFF MDI (Supplementary Table 6). The peak change in IC for all doses of GFF MDI were significantly larger than those for GP MDI 18 µg and open-label tiotropium, but not FF MDI 9.6 µg.

All doses of GFF MDI, as well as open-label tiotropium 18 µg, produced increases from baseline of ≥ 0.110 L in mean evening 12-h

post-dose trough FEV₁ with the largest increase noted for GFF MDI 18/9.6 µg (0.196 L), while the increases with GP MDI 18 µg and FF MDI 9.6 µg were <0.100 L (Supplementary Table 7). The two highest doses of GFF MDI yielded changes that were significantly greater than those resulting from GP MDI 18 µg, and both of these doses of GFF MDI, as well as the 2.4/9.6 µg dose, led to changes that were significantly greater than those for FF MDI 9.6 µg.

3.3. Safety

Treatment-emergent AEs (TEAEs) reported by $\geq 2\%$ of all patients by treatment are shown for preferred terms within system organ classes (Table 2). The most common TEAEs were dry mouth and tremor. Dry mouth was reported by patients in all treatment arms, with the largest percentage of this AE being reported for GP MDI 18 µg (12.1%) and open-label tiotropium 18 µg (8.5%) with numerically smaller percentages of reports for all doses of the combination product. Tremor was reported by 1.5–7.1% of patients

Table 1
Baseline demographics and patient characteristics (ITT population).

	GFF MDI					GP MDI	FF MDI	Open-label tiotropium
	18/9.6 µg N = 71	9/9.6 µg N = 70	4.6/9.6 µg N = 67	2.4/9.6 µg N = 71	1.2/9.6 µg N = 68	18 µg N = 66	9.6 µg N = 73	18 µg N = 71
Age, years								
Mean (SD)	63.0 (8.5)	63.6 (8.5)	62.3 (8.5)	62.0 (9.2)	64.5 (8.6)	63.3 (8.2)	61.8 (8.9)	62.9 (7.5)
Gender, n (%)								
Male	34 (47.9)	39 (55.7)	29 (43.3)	37 (52.1)	35 (51.5)	40 (60.6)	35 (47.9)	42 (59.2)
Race, n (%)								
White	70 (98.6)	68 (97.1)	66 (98.5)	69 (97.2)	65 (95.6)	60 (90.9)	68 (93.2)	66 (93.0)
Other	1 (1.4)	2 (2.9)	1 (1.5)	2 (2.8)	3 (4.4)	6 (9.1)	5 (6.9)	5 (7.0)
Smoking status, n (%)								
Current	32 (45.1)	34 (48.6)	36 (53.7)	35 (49.3)	30 (44.1)	31 (47.0)	34 (46.6)	44 (62.0)
Former	39 (54.9)	36 (51.4)	31 (46.3)	36 (50.7)	38 (55.9)	35 (53.0)	39 (53.4)	27 (38.0)
Duration of COPD, years								
Mean (SD)	7.9 (6.3)	8.2 (6.3)	5.5 (4.1)	8.1 (5.0)	7.9 (6.4)	8.1 (6.3)	6.9 (4.8)	7.0 (5.3)
CAT score								
Mean (SD)	19.0 (7.5)	18.5 (7.6)	19.3 (7.0)	18.7 (6.8)	18.3 (7.1)	19.3 (7.7)	19.5 (7.0)	19.4 (6.4)
Pre-bronchodilator FEV₁, % predicted^a								
Mean (SD)	49.9 (13.4)	49.3 (14.2)	51.1 (13.7)	50.1 (14.2)	49.2 (12.8)	48.0 (13.4)	50.7 (13.5)	47.5 (14.0)
Post-bronchodilator percent predicted FEV₁, % predicted^a								
Mean (SD)	55.3 (14.0)	54.7 (14.6)	56.0 (14.4)	56.7 (14.4)	54.2 (14.0)	52.6 (14.3)	56.7 (13.9)	53.2 (14.8)
Pre-bronchodilator FEV₁, L^a								
Mean (SD)	1.4 (0.5)	1.5 (0.5)	1.4 (0.5)	1.5 (0.5)	1.4 (0.5)	1.4 (0.6)	1.5 (0.6)	1.4 (0.5)
Post-bronchodilator FEV₁, L^a								
Mean (SD)	1.6 (0.5)	1.6 (0.5)	1.6 (0.5)	1.7 (0.6)	1.5 (0.5)	1.6 (0.6)	1.7 (0.6)	1.6 (0.6)
Baseline IC, L^a								
Mean (SD)	2.0 (0.5)	2.1 (0.6)	1.9 (0.5)	2.0 (0.6)	2.0 (0.6)	2.1 (0.6)	2.1 (0.7)	2.0 (0.6)

CAT, COPD Assessment Test; COPD, chronic obstructive pulmonary disease; FEV₁, forced expiratory volume in 1 s; FF, formoterol fumarate; GFF, glycopyrrrolate/formoterol fumarate; GP, glycopyrrrolate; IC, inspiratory capacity; MDI, metered dose inhaler; mITT, modified intent-to-treat; SD, standard deviation.

^a Assessments performed at screening, mITT population.

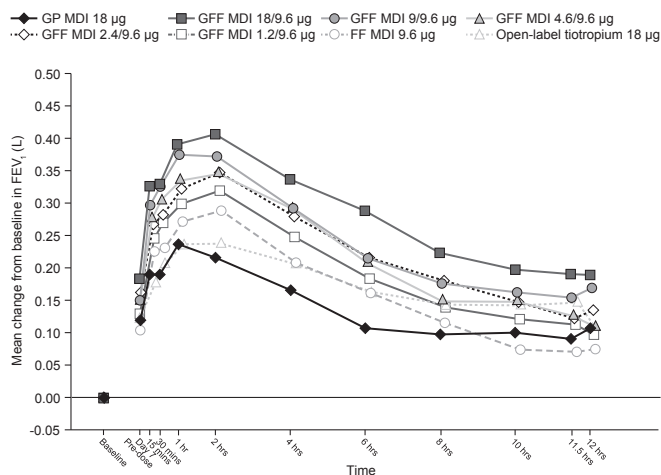


Fig. 2. Adjusted mean change from baseline in FEV₁ AUC_{0–12} post-dose on Day 7 (mITT population). FEV₁, forced expiratory volume in 1 s; FF, formoterol fumarate; GFF, glycopyrrrolate/formoterol fumarate; GP, glycopyrrrolate; MDI, metered dose inhaler; mITT, modified intent-to-treat.

while they received GFF MDI (all doses except the highest dose) or FF MDI alone. No clinically relevant changes from baseline in vital signs, laboratory results or ECGs were noted among the treatment groups. Six patients experienced SAEs (cardio-respiratory arrest, sudden death, transient ischemic attack, spinal compression fracture, pneumothorax, and tachycardia), all of which resulted in study withdrawal. These were evenly distributed across the treatment arms and were all considered unrelated to study treatment. An additional seven patients were withdrawn from the study due to TEAEs (heart rate increased, ECG QT prolonged, bronchitis, and COPD exacerbation), and one patient was withdrawn 9 days after the end of Treatment Period 4 due to pneumonia. Only the case of

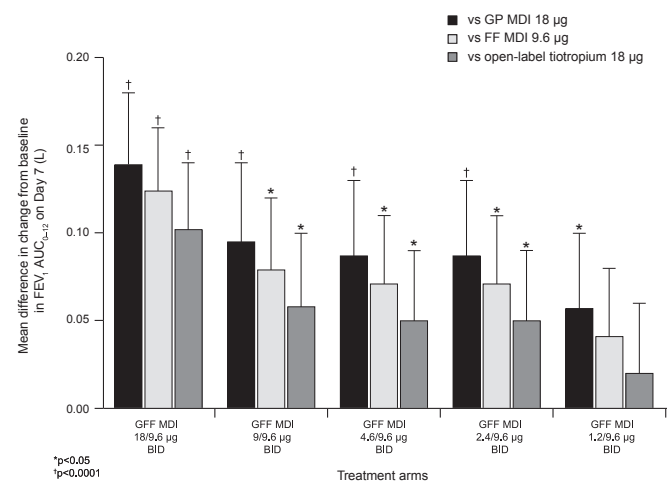


Fig. 3. Adjusted least squares mean difference (95% CI) in FEV₁ AUC_{0–12} with GFF MDI versus monocomponent MDIs and open-label tiotropium, Day 7 (mITT population). BID, twice daily; FEV₁ AUC_{0–12}, forced expiratory volume in 1 s, area under the curve from 0 to 12 h; FF, formoterol fumarate; GFF, glycopyrrrolate/formoterol fumarate; GP, glycopyrrrolate; MDI, metered dose inhaler.

ECG QT prolonged was considered by the Principal Investigator to be related to study treatment (GFF MDI 9/9.6 µg). Two SAEs resulted in death, neither of which was deemed to be treatment-related by the Principal Investigator. One death was due to cardio-pulmonary arrest in a patient with underlying cardiovascular risk factors (GFF MDI 1.2/9.6 µg) and the other fatal SAE was a sudden death of unknown cause (FF MDI 9.6 µg).

4. Discussion

Key findings from this dose-ranging study revealed that all

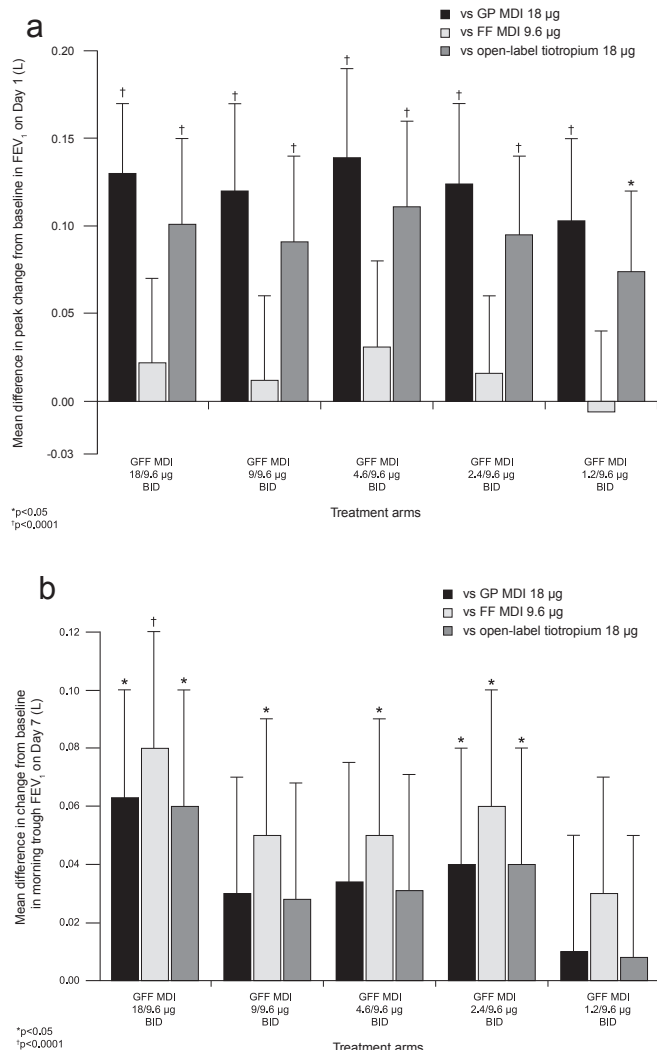


Fig. 4. a) Adjusted least squares mean difference (95% CI) in peak change from baseline in FEV₁ with GFF MDI versus monocomponent MDIs and open-label tiotropium on Day 1 (mITT population). b) Least squares mean difference (95% CI) in change from baseline in morning pre-dose trough FEV₁ with GFF MDI versus monocomponent MDIs and open-label tiotropium on Day 7 (mITT population). BID, twice daily; FEV₁, forced expiratory volume in 1 s; FF, formoterol fumarate; GFF, glycopyrrrolate/formoterol fumarate; GP, glycopyrrrolate; MDI, metered dose inhaler; mITT, modified intent-to-treat.

doses of the LAMA GP evaluated (except for the lowest dose of 1.2 µg) in combination with the LABA FF (9.6 µg) provided greater bronchodilation compared with the individual components (GP MDI 18 µg and FF MDI 9.6 µg) as well as with open-label tiotropium 18 µg. Within this range of doses, the highest dose of GP (18 µg) in the dual-bronchodilator combination (GFF MDI) consistently showed greater bronchodilation than the lower doses as reflected in the improvements in FEV₁ AUC_{0–12} and both morning and evening trough FEV₁ on the seventh day of treatment. Moreover, the improvements in the integrated mean FEV₁ over the dosing interval (FEV₁ AUC_{0–12}) resulting from GFF MDI 18/9.6 µg over that produced by the monocomponents as well as by open-label tiotropium exceeded the pre-specified threshold for FEV₁ of 0.080 L [36,37].

Peak changes in bronchodilation from baseline for all doses of GFF MDI versus GP MDI 18 µg also exceeded the 0.080 L threshold for FEV₁. However the incremental benefits achieved with GFF MDI versus FF MDI 9.6 µg were lower than those achieved versus GP

MDI 18 µg, and only exceeded the threshold of 0.080 L with GFF MDI 18/9.6 µg.

The onset of bronchodilation in the majority of patients receiving any of the doses of GFF MDI was within 15 min, which was faster than the onset observed for the anticholinergic bronchodilators singly but generally comparable to the time of onset following FF MDI. Although less than a third of patients receiving GP MDI in this study had an onset of action within 15 min, more recent studies have shown the onset of bronchodilation with GP MDI is statistically significantly different from placebo at 5 min [38].

IC is a measure of lung hyperinflation [39] and all doses of GFF MDI (with the exception of GFF 9/9.6 µg) produced significantly greater improvements in IC than GP MDI or open-label tiotropium, indicating that a LAMA/LABA FDC may reduce hyperinflation more effectively than a LAMA alone. As lung hyperinflation contributes to the characteristic symptoms of COPD, such as dyspnea and exercise intolerance [40], the results of this study indicate a further physiological effect of GFF MDI therapy that could have the potential for reducing symptom burden.

While GFF MDI augmented bronchodilation over that achieved with the single bronchodilators, the overall incidence of AEs for all doses of GFF MDI evaluated was not different from that of the individual components of GP MDI 18 µg and FF MDI 9.6 µg or open-label tiotropium. Moreover, the AEs observed for all doses of GFF MDI were consistent with the known AE profile of each class of bronchodilator [19,41–43]. These dose-ranging findings further support the choice of GP 18 µg with regard to both efficacy and safety as the optimal dose to combine with FF 9.6 µg in Phase III clinical trials for assessment of the longer-term clinical benefits and safety of the combination in comparison with the single components.

No clinically-significant cardiovascular safety signal was observed during the 1-week treatment periods with any dose of GFF MDI in this dose-ranging study. Future longer-term Phase III studies and post-marketing pharmacovigilance should examine the potential for adverse cardiovascular effects with this LAMA/LABA combination.

Currently available LAMA/LABA FDC products include: aclidinium/formoterol, umeclidinium/vilanterol, and glycopyrronium/indacaterol that are administered via DPI, and olodaterol/tiotropium, which is administered via SMI [1]. MDIs can be used by patients who may struggle due to severe airflow limitation to activate a DPI [44,45] and are currently the most commonly used devices overall for respiratory drug delivery [46]. Therefore, GFF MDI may fulfil this opportunity to widen the choice of inhalers available to patients by providing an MDI that can deliver a LAMA/LABA FDC. It is not known whether there are clinically important differences in efficacy between the various LAMA/LABA FDCs and head-to-head trials are needed to provide these comparisons.

There are several limitations to this study that should be considered when interpreting the findings. Patients received the treatments for only 7 days, so further studies are required to examine whether the improvements in lung function that GFF MDI provided for patients is maintained over the longer term. The patient cohort included patients with moderate-to-severe COPD, so the efficacy and safety of GFF MDI in patients with very severe COPD remains to be determined. The active comparator, tiotropium, was open-label, which may lead to bias in this treatment group. Finally, as COPD symptoms were not assessed, it was not possible to determine whether the lung function improvements that GFF MDI demonstrated versus GP MDI, FF MDI, and open-label tiotropium resulted in improvements in the patients' symptom burden.

Table 2Treatment-emergent adverse events reported for $\geq 2\%$ of all patients (safety population).

	GFF MDI					GP MDI	FF MDI	Open-label tiotropium
	18/9.6 μg	9/9.6 μg	4.6/9.6 μg	2.4/9.6 μg	1.2/9.6 μg	18 μg	9.6 μg	18 μg
	N = 71	N = 70	N = 67	N = 71	N = 68	N = 66	N = 73	N = 71
Dry mouth	2 (2.8)	3 (4.3)	3 (4.5)	5 (7.0)	1 (1.5)	8 (12.1)	6 (8.2)	6 (8.5)
Tremor	0	5 (7.1)	2 (3.0)	4 (5.6)	1 (1.5)	0	2 (2.7)	0
Vomiting	1 (1.4)	1 (1.4)	0	0	0	3 (4.5)	0	1 (1.4)
COPD	3 (4.2)	1 (1.4)	0	0	0	0	1 (1.4)	1 (1.4)
Cough	2 (2.8)	0	1 (1.5)	0	0	0	2 (2.7)	1 (1.4)
Nasopharyngitis	1 (1.4)	1 (1.4)	1 (1.5)	2 (2.8)	0	0	0	1 (1.4)
Diarrhea	0	1 (1.4)	1 (1.5)	1 (1.4)	0	1 (1.5)	1 (1.4)	0
URTI	2 (2.8)	1 (1.4)	2 (3.0)	0	0	0	0	0
Headache	0	0	1 (1.5)	0	1 (1.5)	1 (1.5)	2 (2.7)	0
Dyspnea	0	0	1 (1.5)	1 (1.4)	1 (1.5)	0	1 (1.4)	0
Nasal congestion	0	1 (1.4)	1 (1.5)	0	0	2 (3.0)	0	0
Muscle spasms	0	1 (1.4)	1 (1.5)	1 (1.4)	0	0	1 (1.4)	0
Hyperkalemia	0	1 (1.4)	0	1 (1.4)	0	2 (3.0)	0	2 (2.8)
Contusion	0	2 (2.9)	0	1 (1.4)	0	0	1 (1.4)	0

Data shown as n (%).

COPD, chronic obstructive pulmonary disease; FF, formoterol fumarate; GFF, glycopyrrolate/formoterol fumarate; GP, glycopyrrolate; MDI, metered dose inhaler; URTI, upper respiratory tract infection.

5. Summary

In a study designed to evaluate the efficacy and safety of five different doses of GP (18, 9, 4.6, 2.4 and 1.2 μg) in a FDC with FF (9.6 μg), the highest dose of GFF MDI (i.e. GFF 18/9.6 μg) consistently showed the greatest improvement over GP MDI 18 μg and FF MDI 9.6 μg singly, as well as over open-label tiotropium, both in mean bronchodilation over the dosing interval (AUC_{0-12}), and in the morning trough FEV_1 compared with the lower doses of GP in the combination. Moreover, the safety profile of GFF MDI at all doses studied was similar to that of the single agents. These findings support the selection of GP 18 μg as the optimal dose to combine with FF 9.6 μg for advancement into Phase III clinical trials of GFF MDI.

List of principal investigators

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Declaration of funding interests

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Conflict of interest disclosures

Dr. Tashkin has received grants from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Sunovion; has been a member of advisory boards for AstraZeneca, Mylan, Novartis, and Sunovion; and has served as a speaker for AstraZeneca, Boehringer Ingelheim and Sunovion.

Dr. Martinez reports personal fees from Amgen, AstraZeneca, Axon, Bioscale, Boehringer Ingelheim, Carden Jennings, CSA Medical, Ikaria/Bellerophon, Genentech, Forest, GlaxoSmithKline, Janssen, Merck, Novartis, Nycomed/Takeda, Pearl Therapeutics Inc., Pfizer, Roche, Sunovion, Theravance, and Unity Biotechnology. He has delivered CME programs for Annenberg, California Society for Allergy and Immunology, CME Incite, Haymarket Communications, Inova Health System, Integrity, InThought, Miller Medical,

National Association for Continuing Education, Paradigm, Peer Voice, St. John's Hospital, St. Mary's Hospital, UpToDate, and Western Society of Allergy and Immunology. He has participated on steering committees for GlaxoSmithKline and Nycomed/Takeda. He received royalty fees from Informa. He has spoken on behalf of AstraZeneca and Nycomed/Takeda. He is currently a member of the GOLD Scientific Committee.

Dr. Rodriguez-Roisin has received grants/research support from Almirall and Menarini, and speaker and/or consultation fees from Almirall, AstraZeneca, Boehringer Ingelheim, Ferrer, Menarini, Novartis, Pearl Therapeutics Inc., Takeda, and Teva. He is currently a member of the GOLD Scientific Committee and chair of the GOLD Board of Directors.

Charles Fogarty is a consultant and investigator for Pearl Therapeutics, Inc.

Dr. Gotfried has received research support from Boehringer Ingelheim, GlaxoSmithKline, Novartis, Pearl Therapeutics Inc., Sunovion, and Theravance. He has also served as a speaker for Boehringer Ingelheim and GlaxoSmithKline.

Michael Denenberg and Gregory Gottschlich have no conflicts of interest to declare.

Dr. Donohue has served on Data and Safety Monitoring Boards for AstraZeneca (Pearl Therapeutics Inc.), Boehringer Ingelheim, Gilead, GlaxoSmithKline, Novartis, and Teva. He has also acted as a consultant for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Mylan, Novartis, and Sunovion.

Chad Orevillo, Patrick Darken, Earl St Rose, Shannon Strom, Tracey Fischer, Michael Golden, and Colin Reisner are employees of Pearl Therapeutics, Inc.

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Dr. Tashkin wrote the first draft of the manuscript.

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Co-Suspension is a trademark of the AstraZeneca group of companies.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2016.09.012>.

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